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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

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27

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n N .	Applicant(s)	
	09/216,062	GUO, YAJUN	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE f this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/2/02 & 2/26/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-49 and 53-110* is/are pending in the application.

4a) Of the above claim(s) *54,55,63-65,67,68,75-78,80,82,83,96-98,100 and 101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-49,53,56-62,66,69-74,79,81,84-95,99 and 102-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

1. Applicant's amendments filed 8/2/02 (Paper No. 22) and 2/26/02 (Paper No. 18) and Applicant's response filed 12/9/02 (Paper No. 26) are acknowledged and have been entered.

2. Applicant's election of the species of hepatocellular carcinoma cells, bispecific antibody for 4-1BB/gp95 and TNF-alpha and IFN-gamma treated cells and TNF-alpha and IFN-gamma in Paper No. 26 is acknowledged. Because the Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 45-49, 53, 56-62, 65-74, 79, 81, 84-96, 99 and 102-110 read on the elected species enunciated above.

Accordingly, claims 54, 55, 63-65, 67, 68,75-78, 80, 82, 83, 96-98, 100 and 101 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 45-49, 53, 56-62, 66, 69-74, 79, 81, 84-95, 99 and 102-110 are currently being examined.

In view of Applicant's amendments filed 8/2/02 and 2/26/02 the following rejections remain

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 45-49, 53, 56-62, 66, 69-74, 79, 81, 84-95, 99 and 102-110 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed immunogenic composition comprising an antibodies with one or more antigen binding sites for one or more gp55, gp95, gp115 or gp210

antigens on the surface of one or more target hepatocellular carcinoma cells, lymphoma cells, colon carcinoma cells or gastric cancer cells and the method of preparing the said composition.

The instant claims encompass antibodies which have antigen binding sites for any glycoprotein antigen on the surface of the said target cells which is of the size 55kDa, 95kDa, 115kDa or 210kDa, i.e., "gp55", "gp95", "gp115" or "gp210". There is insufficient disclosure in the specification on said composition and a method of preparing the said composition.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood , 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of an antigen "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description ... requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; Id. at 1170, 25 USPQ2d at 1606.

The specification discloses (on page 7 at lines 15-16) that said binding sites can be directed towards CD28, 4-1BB, CTLA-4 or (on page 7 at lines 6-9) which can activate T cell costimulatory pathways through T cell surface proteins. The specification discloses bispecific antibodies CD28:gp55, CD28:gp95, CD28:gp115 and CD28:gp210 (figures and Example 2). The specification further discloses CD28:gp55 armed hepa 1-6 (hepatoma tumor cells), EL-4 (lymphoma cells) or SMCC-1 (colon carcinoma cells) (Examples 7, 8). The specification also discloses EL-4 tumor cell armed -Bi-Mab anti-gp115:anti-4-1BB (4-1BB is a glycoprotein expressed on primed T CD4+ and CD8+ T cells) (Example 8).

The instant specification discloses (on page 45 at lines 10-23) that weakly or non-immunogenic autologous target cells are treated in order to amplify primary and costimulatory T cell activation signals in the cells, and bispecific monoclonal antibodies capable of binding to one or more antigens on the treated cells and to one or more T cell activation costimulatory molecules on the surface of T cells are attached. The instant specification discloses (on pages 31-34, 41-42 and 44-45) use of the invention to cause hepa 1-6 hepatoma, SMCC-1 or EL-4 tumor cell regression in mice or to retard tumor formation rate. The specification also discloses human clinical data on human hepatocellular carcinoma and colon cancer (Example

16). The specification further discloses that four monoclonal antibodies were produced which reacted with hepa 1-6 cells and recognized either a 55 kDa, 95 kDa, 115kDa or 210 kDa glycoprotein expressed on most tumor cells as determined by immunoprecipitation. The specification discloses that the said monoclonal antibodies were designated as anti-gp55, anti-gp95 and anti-gp210, respectively (page 24 at lines 29-31 and page 25 at lines 1-6). The specification also discloses that bispecific monoclonal antibodies were produced from these antibodies (page 25 at lines 7-17).

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. However, a generic statement such as "gp55", "gp95", "gp115" or "gp210", without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being a glycoprotein of 55, 95, 115 or 210 kDa size. It does not specifically define any of the glycoproteins that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others, other than size. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. Many such species may be 55, 95, 115 or 210 kDa in size. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Since the disclosure fails to provide sufficient relevant identifying characteristics that identify members of the genus, and given the broad genus claimed, the disclosure of an antibody to a protein of 55, 95, 115 or 210 kDa on the surface of one type of hepatocellular carcinoma cell line is insufficient to describe the genus as broadly claimed. One of skill in the art would not have recognized that Applicant was in possession of the invention claimed in the instant claims.

Applicant's arguments in the amendment filed 2/26/02 have been fully considered but are not persuasive.

It is the Applicant's position (beginning on page 4 of the said amendment) that the chemical identity of the gp glycoproteins recited in the instant claims are clearly described by the process of isolation, that the method of preparing antibodies to the gp glycoproteins is disclosed by the instant specification, that the gp nomenclature is a convenience only and not an intended limitation of the claims.

It is the Examiner's position that the Applicant's arguments are moot for the reasons of record. In addition, it is the Examiner's position that the gp glycoproteins recited in the instant claims encompass multiple proteins of a designated molecular weight on cancer cells of a certain type which may be a cell line, a clone, freshly isolated cells, cultured cells which may express different proteins on their surface depending on their environment and which may express multiple proteins of the same or closely similar molecular weight as determined by Mr on gels.

5. Claims 45-49, 53, 56-62, 66, 69-74, 79, 81, 84-95, 99 and 102-110 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and/or use the instant invention. The claimed method of making a composition and the said composition comprising one or more hepatocellular carcinoma, lymphoma or colon carcinoma or gastric cancer cells and one or more antibodies comprising one or more binding sites for one or more gp55, gp95, gp115 or gp120 antigens on the surface of one or more of the autologous target cells encompasses: (1) making and using antibodies to any 55, 95, 115 or 210 kDa glycoprotein, i.e., "gp55", "gp95", "gp115" or "gp210" on the surface of any isolated autologous target hepatocellular carcinoma, lymphoma, colon or gastric carcinoma cell. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a composition which comprises an antibody with a specificity against any cell surface protein on any of the said target cells recited in the instant claims. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and/or used.

The specification further discloses that four monoclonal antibodies were produced which reacted with hepa 1-6 cells and recognized either a 55 kDa, 95 kDa, 115kDa or 210 kDa glycoprotein expressed on most tumor cells as determined by immunoprecipitation. The specification discloses that the said monoclonal antibodies were designated as anti-gp55, anti-gp95 and anti-gp210, respectively (page 24 at lines 29-31 and page 25 at lines 1-6). The specification also discloses that bispecific monoclonal antibodies were produced from these antibodies (page 25 at lines 7-17). The instant specification discloses working examples for (on pages 41-42 and 44-45) use of the invention (irradiated tumor cells armed with gp115xCD28 bispecific mAb) to cause hepa 1-6 hepatoma tumor cell regression in mice and to cause tumor regression of SMCC-1 colon carcinoma in mice, respectively. The specification also discloses human clinical data on human hepatocellular carcinoma and colon cancer, but does not specify what bispecific mAb were used (Example 16).

The specification does not disclose that the said monoclonal antibodies against a 55, 95, 115 or 210 kDa glycoprotein on HEPA 1-6 cells is readily available to the public, nor does the specification disclose a repeatable method for obtaining the said monoclonal antibodies. In addition the specification does not disclose that the bispecific antibodies produced which utilize

the said monoclonal (monospecific) antibodies are readily available to the public, nor does the specification disclose a repeatable method for obtaining the said bispecific antibodies except for reference to journal articles on page 25 at lines 15-17. It is apparent that the said antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. There is no disclosure in the specification of the particular epitope, nor the sequence of the protein recognized by the said antibody, and therefore a routineer would not be able to produce the said antibodies based on the disclosure of the specification. If the said antibodies are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the hybridoma producing the said antibody. See 37 CFR 1.802.

Evidentiary reference Periera et al teach "GP55" which is a viral envelope glycoprotein from SFFV (spleen focus forming virus) required for leukemogenicity (especially page 5106), i.e., the "GP55" of Periera et al is an example of a viral glycoprotein that is tumorigenic and is of the same size as the "GP55" protein on the surface of HEPA 1-6 cells in the instant specification, but which may be a different glycoprotein.

There is insufficient guidance in the specification as to how to make and/or use the instant invention, including reliance on monoclonal antibodies made to a glycoprotein of 55, 95, 115 or 120 kDa size on the surface of the HEPA 1-6 hepatocellular carcinoma cell line. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments in the amendment filed 2/26/02 have been fully considered but are not persuasive.

It is the Applicant's position (beginning on page 6 of the said amendment) that the amendment to claims 45 and 70 do not recite an antibody with a specificity against any cell surface protein and because the bridging molecules are attached to the tumor cells in vitro prior to treating a patient in vivo, the need for unique specificity is eliminated, that sufficient disclosure exists in the specification enabling one of skill in the art to isolate an appropriate binding site associated with antigens located on the surface of the tumor cells, and that anti-CD28 antibodies are disclosed as the bispecific antibodies in the specification, that the gp nomenclature is purely for convenience and not intended as a structural limitation.

It is the Examiner's position that the Applicant's arguments are moot for the reasons of record. In addition, the bispecific antibodies recited in the instant claims comprise a binding site not only for CD28, but also a binding site for a gp antigen, which is a designation for a molecular weight of a protein on the surface of a cell. In addition, the claims encompass a bispecific antibody with a binding site for a protein of undisclosed structure and only characterized by an approximate size, on cancer cells which can be a cell line, a clone, freshly isolated cells or cultured cells which differ in the types of proteins they express on their surface.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 70-74, 79, 81, 84-95, 99 and 102-110 stand are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 103-139 of copending Application No. 08/872,527. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the 08/872,527 application are encompassed by the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 45-49, 53, 56-62, 66, 69-74, 79, 81, 84-95, 99 and 102-110 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 45, 58, 65-68, 70, 87, 89, 98-101 are indefinite in the recitation of "gp55, gp95, gp115 or gp120" antigens or antibodies comprising binding sites to the said "gp55, gp95, gp115 or gp120" antigens because the characteristics of the said gp55, gp95, gp115 and gp210 antigens and hence, that of the said antibodies, are not known. The use of "gp55", "gp95", "gp115" and "gp120" as the sole means of identifying the protein to which the claimed antibody is specific renders the claim indefinite because "gp55", "gp95", "gp115" and "gp120" are merely laboratory designations which do not clearly define the claimed product,

since the said designation is merely a characterization of a protein by size and may refer to many different proteins.

Applicant's arguments in the amendment filed 2/26/02 have been fully considered but are not persuasive.

It is the Applicant's position (beginning on page 8 of the said amendment) that the designation "gp" is for convenience.

It is the Examiner's position with regard to the "gp" designation that the position enunciated above in #5 and #6 supra apply here.

The following are new grounds of rejection necessitated by Applicant's amendments filed 8/2/02 and 12-26-02.

10. Claims 45-49, 53, 56-62, 66, 69 and 99 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 46-49 and 58 recite the limitation "said one or more hepatocellular carcinoma cells. There is insufficient antecedent basis for this limitation in the claims.

b. Claim 56 recites the limitation "one or more". There is insufficient antecedent basis for this limitation in the claim.

c. Claim 45 is indefinite in the recitation of "a bispecific monoclonal antibodies" because it is not clear what is meant.

d. Claim 66 recites the limitation "one or more gp55...". There is insufficient antecedent basis for this limitation in the claim.

e. Claims 66 and 99 are indefinite in the recitation of "antigen comprises gp95 antigens" because it is not clear what is meant.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will

expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is 703-308-0061. The examiner can normally be reached on Monday and Thursday from 11 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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March 6, 2003

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